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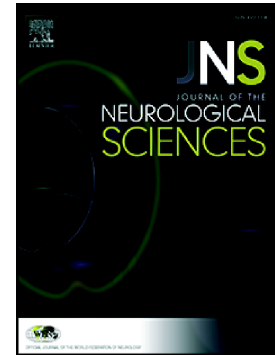
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Primary glioblastoma multiforme of the conus medullaris with leptomeningeal metastasis

Case report

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MANUSCRIPT

Dear Editor,

Most spinal tumours are benign, with only 10-15% showing high-grade features such as endothelial proliferation or necrosis upon histological examination [5]. Glioblastoma multiforme (GBM) represents only a subset of these, and is radically less common in the spinal cord than it is in the brain, representing only 1.4% of intraspinal tumours [5]. GBM of the conus medullaris is even rarer, having been reported in only a handful of case reports, and represents unique challenges in terms of diagnosis and management. Here, we report such a case, review the limited available evidence and discuss the management of this rare malignancy.

Case

A previously-well 31-year-old male presented with a three-week history of progressive left leg weakness and altered sensation. He denied any bowel or bladder dysfunction, and had normal perineal sensation. Subsequent MRI spine showed a T2 hyperintense lesion of the conus medullaris, expanding the cord, with a 'tail' extending rostrally to T9. There were normal appearances of the brain, cervical and upper thoracic spinal cord. This lesion was initially felt likely to be inflammatory although patchy enhancement also raised the possibility of a neoplastic lesion. A trial of steroids was commenced and the possibility of biopsy discussed. However, the risks of this procedure were felt to outweigh the benefits at this time, and it was decided to monitor the lesion clinically with regular follow-up. Unfortunately, 4 months later, the patient re-presented with further deterioration of his neurological function, including right leg weakness and urinary retention. Given his acute decompensation, it was felt prudent to proceed to surgery to decompress the thecal sac, debulk the lesion and obtain tissue for histological analysis. This was performed with intraoperative neuromonitoring and GliolanTM assistance (although there was no intra-operative fluorescence). Histology revealed a high-grade glioma, with nuclear atypia, and an abundance of mitotic figures suggestive of GBM. It contained non-mutated copies of *IDH1* and *ATRX*. Following surgery, he was neurologically unchanged and was discharged home. He subsequently underwent a 6-week course of radiotherapy (54Gy in 30 fractions) combined with temozolomide chemotherapy, which was well-tolerated. Following this, he was planned for 6 cycles of temozolomide adjuvant chemotherapy. However, following his fifth cycle, he deteriorated with severe nausea and vomiting and was found to have intracranial leptomeningeal infiltration, although the original spinal tumour was stable. His

dose of dexamethasone was increased, and his symptoms resolved. His chemotherapy was revised to single agent lomustine combined with bevacizumab. Unfortunately, two months later he was admitted in status epilepticus which proved a terminal event 14 months after his initial diagnosis.



Figure 1 Pre-operative and follow-up MRI images. A and B: Pre-operative sagittal and axial T1-weighted images post-gadolinium; C and D: Pre-operative T2-weighted images; E and F: Post-operative T1-weighted images post-gadolinium; G and H: T1-weighted images post-gadolinium at 6 months following subtotal resection.

Discussion

Glioblastoma multiforme is an aggressive, high-grade malignancy of glial cell origin. Conus GBMs present most commonly with back pain and sensory or motor disturbance. The MRI appearances of conus GBMs are highly variable but tend to include T2 hyperintensity and T1 hypointensity with homogeneous enhancement, although enhancement can be patchy if necrosis or cyst formation is a prominent feature.

The mainstay of treatment is 'safe surgical resection' followed by adjuvant therapy, however, the best modality for adjuvant treatment remains under debate. Our patient received chemotherapy concomitantly with radiotherapy for six weeks, and was intended to have six 28-day cycles of adjuvant chemotherapy following this. In addition to focal radiotherapy and chemotherapy, a number of authors also recommend whole craniospinal axis irradiation, owing to the possibility of intracranial/leptomeningeal dissemination [1]. The high radiation doses required to obtain whole neural axis control for GBM, however, is a cause for concern. Two previous cases in the literature have received temozolomide for conus GBM and another received a combination of procarbazine, lomustine and vincristine [4, 8, 12]. This latter patient survived for a prolonged period (67 months) perhaps casting doubt on the accuracy of the original histological diagnosis. The survival of the two patients who received temozolomide was not reported.

In addition to the literature on conus GBMs, there is a larger literature pertaining to adjuvant therapy in spinal GBM in general, although this still lacks prospective studies. Allen and colleagues demonstrated a favourable 5-year survival rate of 54% with a combination of 8 chemotherapy drugs in 13 children with high-grade gliomas [1]. Kaley and colleagues addressed the use of adjuvant temozolomide or bevacizumab (in 8 and 6 patients, respectively) and showed clinical and radiological improvement with both agents [6]. Survival to 26 months has also been shown with the use of intrathecal β -interferon in addition to radiotherapy [2]. However, other studies have failed to identify adjuvant chemotherapy as a prognostic factor in spinal GBM [9, 13], probably owing to the small size and retrospective nature of all of the studies. Rare long-term survivors have been seen with 'radiocordectomy', in which radiation above the tolerance of the spinal cord is administered at the tumour bed, although this should be reserved for patients who are already paraplegic. The two reported cases of patients who received this treatment survived for 6 and 12 years respectively [7, 14].

The extent of surgical resection remains debatable in spinal cord GBMs. In contrast to benign tumours of the spine, data to support total macroscopic resection is limited, and this strategy risks post-operative neurological deficit. Raco and colleagues reported that 61% of grade III and IV spinal tumours resected in their series had a poorer neurological function post-operatively [11]. McGirt and colleagues failed to show a relationship between extent of resection and survival in 8 patients with spinal GBM [9]. The recommended approach is therefore to debulk the tumour as far as possible with preservation of neurological function.

Following six months without neurological deterioration, our patient developed intracranial leptomeningeal disease (LMD) despite stable disease at the primary site. Intrathecal chemotherapy has been shown to result in a modest survival benefit (2-4 months) in cases of leptomeningeal spread from a GBM primary, however, it carries with it significant risks of meningitis and myelosuppression [3, 10]. Whole-brain radiotherapy (WBRT) has also been used to treat LMD, and is the standard approach to this complication in malignancies from other sources (for instance, breast cancer). However, there are few reported cases of its use in LMD associated with GBM (possibly due to the poor prognosis LMD confers) and it carries with it the risk of cognitive decline, which may have a detrimental effect on the few remaining months of life. Given the poor prognosis at this point and the potential morbidity associated with WBRT or intrathecal chemotherapy, an alkylated agent was chosen as second-line chemotherapy and bevacizumab initiated due to the presence of significant oedema.

In summary, conus GBM is a rare entity with non-specific imaging characteristics and no well-established treatment protocols. Our experience combined with the limited data from the literature suggests safe, subtotal resection combined with chemo-radiotherapy confers the best outcome.

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Compliance with Ethical Standards

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